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Stereoselective synthesis of 2-azetidinones as cholesterol-absorption inhibitors

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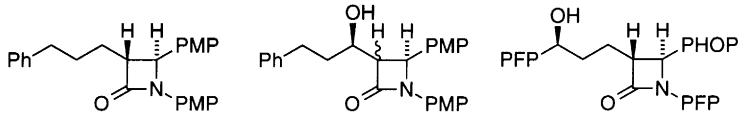
Abstract

The synthesis of two 2-azetidinones possessing powerful cholesterol-absorption inhibition properties has been accomplished by a short and highly stereoselective reaction sequence. The key step is the condensation of the titanium enolate of the easily prepared 2-pyridylthioester (*R*)-**11** with imine **6** which affords the desired β-lactam intermediate in the correct relative and absolute configuration. Conversion to the pharmacologically active compounds is readily accomplished by simple functional group manipulation. © 2000 Elsevier Science Ltd. All rights reserved.

1. Introduction

In addition to their well-recognized properties as antibiotics,[1–3] β-lactams have been recently shown to possess other relevant biological activities as inhibitors of prostate specific antigen,[4] thrombin,[5] human cytomegalovirus protein,[6] human leukocyte elastase,[7] and cholesterol absorption.[8] In particular, azetidinones **1**–**4** (Fig. 1) are potent orally active inhibitors of acyl-CoA, cholesterol acyltransferase, that block absorption of intestinal cholesterol and limit cholesterol ester deposition in the vascular wall.[9,10]



(3*R*,4*S*)-**1** (3′*R*,3*S*,4*S*)-**2** (3′*R*,3*R*,4*S*)-**3** (*S*,3*S*,4*S*)-**4**

Abbreviations: PMP = 4-MeOPh; PFP = 4-FPh; PHOP = 4-HOPh

Fig. 1. Structure of cholesterol absorption inhibiting 2-azetidinones

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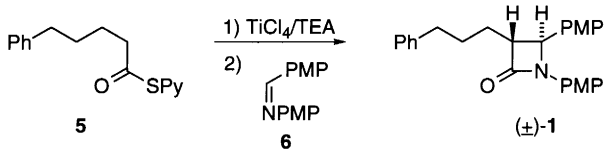
Synthesis of **1**–**4** and congeners both in racemic and enantiomerically enriched form have been published,[8–16] but a margin of improvement for the reported processes does exist. We here report new syntheses of azetidinones (±)-**1**, (3*R*,4*S*)-**1**, and (3′*R*,3*S*,4*S*)-**2**† based on the efficient one-pot preparation of β-lactams by reaction of the titanium enolate[17] of 2-pyridylthioesters with imines that we have developed over the last few years.[18–20]

2. Results and discussion

Racemic **1** was very easily obtained in 91% yield by condensation of the titanium enolate of S-2-pyridylthio-5-phenylvalerate **5** with imine **6** (Scheme 1, PMP=4-methoxyphenyl) in dichloromethane at 0°C. This reaction was completely stereoselective and afforded the product only as the 3,4-*trans* isomer, as determined by 300 MHz ^{1}H NMR analysis of the crude reaction mixture (in β-lactams J_{trans}=1.5–3.0 Hz; J_{cis}=4.0–6.0 Hz).



Abbreviations: Py = 2-Pyridyl; TEA = Triethylamine

Scheme 1. Stereoselective synthesis of racemic 2-azetidinone **1**

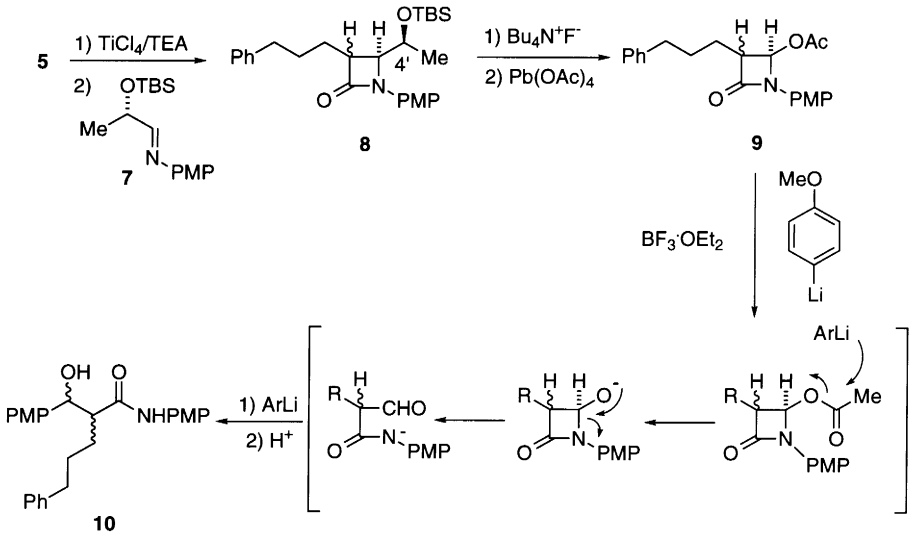
Several approaches can be envisaged in order to obtain **1** in enantiomerically enriched form starting from a pyridylthioester. These involve the use of boron enolates featuring enantiopure boron ligands,[21] and of enantiomerically pure imines[22,23] or thioesters.[22,24] However, reaction of **5** with imine **6,** carried out in the presence of boron trichloride and (1*R*,2*S*)-*N*-methylephedrine,[21] gave the product in extremely low yield.

The use of lactaldehyde-derived imine (*S*)-**7** was also unsuccessful (Scheme 2). Indeed, the titanium enolate of thioester **5** reacted with **7** to give β-lactam **8** in 65% yield as a 85:15 mixture of 3,4-*trans*-4,4′-*syn* and 3,4-*cis*-4,4′-*syn* isomers (see Scheme 2 for numbering). Oxygen deprotection and oxidation with lead tetraacetate[25] gave the 4-acetoxy derivative **9** in 40% unoptimized overall yield.

Reaction of this β-lactam with a variety of aryl nucleophiles, however, failed to produce the desired adduct (3*R*,4*S*)-**1**, probably because the presence of the PMP group at nitrogen in **9** prevents the formation of an endocyclic C–N double bond. The use of a large excess of 4-methoxyphenyllithium in combination with $BF_3 \cdot OEt_2$ led to the formation of adduct **10** (40% yield, 75:25 mixture of diastereoisomers), possibly by the mechanism shown in Scheme 2.

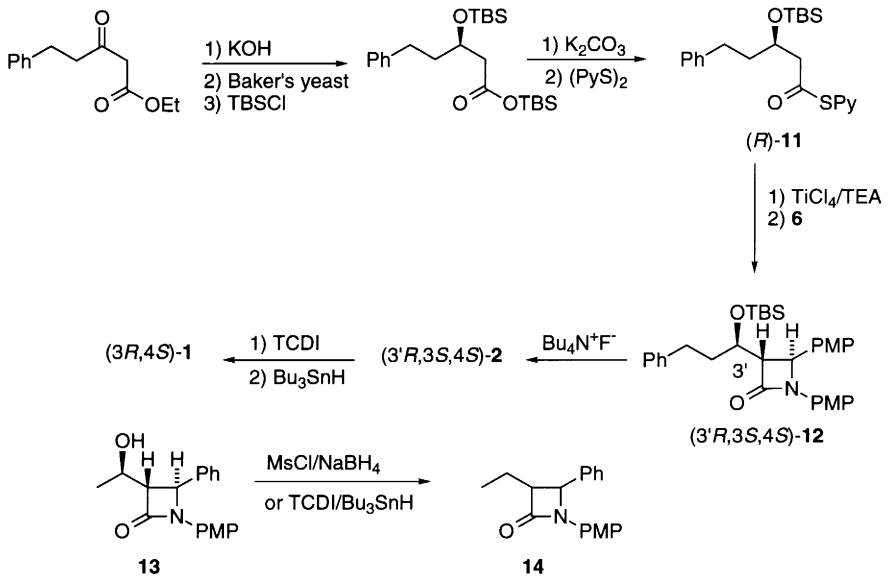
On the basis of these disappointing results and our previous experience,[18–20,22,24] it was decided to use the stereocenter of thioester (*R*)-**11** as the stereodirecting element for the generation of the C-3 and C-4 stereocenters of **1** and **2** (Scheme 3). Compound **11** was synthesized as follows. Ethyl 5-phenyl-3-oxovalerate (obtained in 95% yield from 3-phenylpropanal following a described procedure)[26] was hydrolyzed with KOH. This carboxylate was enzymatically reduced for 7 to 15 days at 25°C[27] with baker's yeast in water buffered with KH_2PO_4. The crude β-hydroxyacid was fully protected with *t*-butyldimethylsilyl chloride,[28] and the crude silyl ester (isolated by rapid filtration through a pad of silica gel) was hydrolyzed[28] and transformed into the desired (*R*)-S-2-pyridylthio-3-(*t*-butyldimethylsilyl)oxy-

† C-3 of **1** and **2** share the same ligand disposition but have different configurational descriptors due to change in the ligand priority.



Scheme 2. Attempted synthesis of (3*R*,4*S*)-**1** from thioester **5** and imine **7**

5-phenylvalerate **11**, that was obtained in 51% overall yield from 3-phenylpropanal after just one chromatographic separation. Enantiomeric excess determination by ^{1}H NMR spectroscopy in the presence of Eu(hfc)$_3$ showed that (*R*)-**11** was ≥96% enantiomerically pure. The (*R*) absolute configuration was tentatively assigned on the basis of the known tendency of baker's yeast reduction of similar substrates to afford the (*R*)-product,[27] and the comparison of the sign of the specific rotation of **11** with that of the known desilylated β-hydroxy 2-pyridylthioester.[29] The subsequent conversion of **11** into azetidinone **2** confirmed the configurational assignment.



Scheme 3. Stereoselective synthesis of (3′*R*,3*S*,4*S*)-**2** and (3*R*,4*S*)-**1** from thioester **11**

Condensation of the titanium enolate of (*R*)-**11** with imine **6** gave adduct **12** in 37% yield‡ as a 94:6 mixture of 3,3′-*anti*-3,4-*trans* and 3,3′-*syn*-3,4-*trans* isomers, as determined by ^{1}H NMR analysis of the crude product (see Scheme 3 for numbering). Pure 3,3′-*anti* **12**, obtained by flash chromatography, was then deprotected with tetrabutylammonium fluoride in THF to afford (3′*R*,3*S*,4*S*)-**2** in quantitative yield.

It should be noted that this represents the first stereoselective synthesis of **2**. So far this product has been prepared only by the poorly stereoselective aldol condensation between the 3-unsubstituted azetidinone and 3-phenylpropanal, followed by HPLC resolution.[13]

The conversion of **2** into **1** requires deoxygenation of C-3′. The conditions of this reaction were established studying the transformation of the model compound **13**[22] to the known β-lactam **14**.[30]

Conversion of **13** into its mesylate ($MeSO_2Cl$, TEA, 94%) followed by $NaBH_4$ reduction in DMSO at 50°C for 15 h[31] gave a 60% yield of **14** (90% based on the recovered mesylate) that unfortunately was isolated as a 60:40 mixture of *trans* and *cis* isomers. Shorter reduction times lowered the yield and led to a similar extent of epimerization, thus showing that the stereomutation occurred before reduction.

A milder method was found in the conversion of **13** into its imidazolylthiocarboxylate (thiocarbonyldiimidazole, refluxing THF, 95%) followed by reaction with Bu_3SnH in DMSO at 90°C for 5 h.[32] By this procedure **14** was obtained as a single *trans* isomer in 50% yield (68% based on the recovered ester). Also in this case, $NaBH_4$ reduction of the activated ester led to extensive epimerization.

Extension of this protocol to azetidinone **2** afforded β-lactam **1** in 51% overall yield (65% based on the recovered activated ester), thus completing the stereoselective synthesis of the desired enantiomerically pure compound from the easily available thioester (*R*)-**11**.

3. Conclusion

In conclusion, a short and highly stereoselective synthesis of the target cholesterol inhibitors **1** and **2** has been accomplished using the easily generated stereocenter of (*R*)-**11** as the only element of stereocontrol. From the preparative point of view, this procedure favorably compares with the existing ones, especially in the case of the synthesis of compound **2**. These results served also to confirm the reliability of the model of stereoselection that was proposed to explain the stereochemical outcome of the condensation of β-silyloxy 2-pyridylthioesters with imines.[22] Extension of a similar protocol to the synthesis of other pharmacologically active 2-azetidinones is currently underway in our laboratories.

4. Experimental

*4.1. Synthesis of S-2-pyridylthio 5-phenylvalerate **5***

To a stirred 1 M solution of commercially available 5-phenylvaleric acid (0.178 g, 1 mmol) in CH_2Cl_2, triphenylphosphine (0.315 g, 1.2 mmol) and dipyridyl disulfide (0.242 g, 1.1 mmol) were added in this order. The solution was stirred at room temperature for 24 h, and the reaction quenched by the addition of water. The organic phase was separated, the aqueous phase was repeatedly extracted with CH_2Cl_2 and the

‡ The low yield of this reaction, for which we do not have any explanation at present, is surprising. For instance, the analog of **11** derived from (*R*)-3-hydroxybutanoic acid (Me instead of Ph-CH_2-CH_2 in **11**) reacted with imines related to **6** in 60 to 95% yield with similar stereoselectivity (see Refs. 22 and 24). Various attempts to improve the yield of **12** (by changing the reagent stoichiometry or the reaction temperature, or by replacing titanium tetrachloride with tin tetrachloride) were unsuccessful. It is also worth mentioning that the Staudinger cycloaddition between the ketene corresponding to **11** and imine **6** carried out in refluxing toluene gave **12** in 40% yield as a 60:40 mixture of 3,3′-*anti*-3,4-*trans* and 3,3′-*syn*-3,4-*trans* isomers.

combined organic phases were dried and concentrated under vacuum. The resulting residue was purified by flash chromatography with a 60:40 hexanes:diethyl ether mixture as eluant to give the product as a pale yellow oil in 98% yield. IR: 1695 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.60 (1H, d, J=4.2 Hz), 7.73 (1H, t, J=5.6 Hz), 7.61 (1H, d, J=5.6 Hz), 7.15–7.27 (6H, m), 2.74 (2H, t, J=7.0 Hz), 2.63 (2H, t, J=7.0 Hz), 1.70–1.75 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.1, 151.3, 150.2, 141.7, 137.2, 130.1, 128.3, 125.7, 123.4, 43.9, 35.4, 30.5, 24.8. Elem. anal.: $C_{16}H_{17}NOS$ requires: C, 70.81; H, 6.31; N, 5.16. Found: C, 70.73; H, 6.23; N, 5.21.

*4.2. Synthesis of (3*R*)-S-2-pyridylthio 3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5-phenylvalerate **11***

Enzymatic reduction: A solution of potassium 5-phenyl-3-oxovalerate (1.0 g) in water (40 mL) was added to a suspension of baker's yeast (25 g), glucose (28 g), $MgSO_4$ (0.03 g), and KH_2PO_4 (0.06 g) in water (40 mL) which was previously stirred at 25°C for 30 min. The resulting suspension was stirred for 1 week, whereupon small portions of glucose were added from time to time. CH_2Cl_2 and 1N HCl were then added so that the aqueous phase had pH 1. The resulting mixture was filtered through Celite, and the filtrate was washed thoroughly with CH_2Cl_2. The organic phase was separated and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic phases were dried and concentrated under vacuum to give the crude product in 99% yield. This was used without further purification.

Silylation: To a stirred 1 M solution of the hydroxyacid (1–2 mmol) in dry CH_2Cl_2, imidazole (5 mol equiv.) and *t*-butyldimethylsilyl chloride (2.5 mol equiv.) were added in this order. After stirring overnight at room temperature the reaction was quenched by the addition of water. The organic phase was separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried and concentrated under vacuum to give the crude product that was filtered through a pad of silica gel with a 95:5 hexane:diethyl ether mixture as eluant. The product was not further purified.

Hydrolysis of the ester: To a solution of the silylester (0.422 g, 1 mmol) in MeOH (13 mL), water (2 mL), and THF (2 mL), K_2CO_3 (0.414 g, 3 mmol) was added. After 2 h the hydrolysis was completed (by TLC) and the solvents were evaporated under vacuum. The residue was dissolved in CH_2Cl_2 (20 mL) and 1N HCl was slowly added with stirring until the aqueous phase had pH 5. The organic phase was separated, washed with water, dried, and concentrated under vacuum. The crude residue was used as such for the following step.

Synthesis of the thioester: To a stirred 1 M solution of the acid in CH_2Cl_2, triphenylphosphine (0.315 g, 1.2 mmol) and dipyridyl disulfide (0.242 g, 1.1 mmol) were added in this order. The solution was stirred at room temperature for 24 h, and the reaction quenched by the addition of water. The organic phase was separated, the aqueous phase was repeatedly extracted with CH_2Cl_2 and the combined organic phases were dried and concentrated under vacuum. The residue was purified by flash chromatography with a 50:50 hexanes:diethyl ether mixture as eluant. The product was a pale yellow oil that had $[\alpha]_D^{23}$ −33.1 (c 0.9 in CH_2Cl_2). IR: 1708 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.63 (1H, d, J=4.2 Hz), 7.77 (1H, t, J=5.6 Hz), 7.63 (1H, d, 5.6 Hz), 7.30 (1H, dd, J=5.6, 4.2 Hz), 7.21–7.28 (5H, m), 4.25–4.30 (1H, m), 2.90 (2H, AB system, J=11.0, 6.5, 5.6 Hz), 2.65–2.70 (2H, m), 190–1.95 (2H, m), 0.93 (9H, s), 0.10 (3H, s), 0.08 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.0, 151.6, 150.3, 141.8, 137.0, 129.8, 128.4, 128.3, 125.6, 125.4, 69.0, 521.7, 39.0, 31.0, 25.8, 18.0, −4.6, −4.7. Elem. anal: $C_{22}H_{31}NO_2SSi$ requires: C, 65.79; H, 7.78; N, 3.49. Found: C, 65.91; H, 7.83; N, 3.39.

Compound **11** was shown to be $\geq$ 96% enantiomerically pure by ^1H NMR analysis carried out in $CDCl_3$ in the presence of the chiral shift reagent Eu(hfc)$_3$ in conditions pre-established on racemic **11**. To this end the signals of the pyridine nucleus were exploited.

4.3. General procedure for the synthesis of β-lactams **1**, **8**, and **12**

To a 0.05 M solution of thioester (1–10 mmol) and $TiCl_4$ (1 M solution in CH_2Cl_2, 1 mol equiv.) in dry CH_2Cl_2 cooled at −78°C and kept under nitrogen, triethylamine (1.1 mol equiv.) was added dropwise. The dark purple solution was stirred at −78°C for 15 min, and a 1 M solution of imine (0.5 mol equiv.) in CH_2Cl_2 was added dropwise. After 5 h stirring at −78°C, the reaction was warmed to room temperature, and the mixture stirred overnight. The reaction was quenched by the addition of a satd solution of $NaHCO_3$ and the resulting slurry was filtered through a Celite cake. The organic phase was separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried and concentrated under vacuum. The residue was dissolved in THF and treated with a 1 M aqueous solution of KOH (2 mol equiv.) to hydrolyze the excess of thioester. This procedure does not alter the diastereoisomeric composition and greatly simplifies the NMR analysis of the crude product. Diethyl ether was added to the mixture and the organic phase was separated, washed with brine, dried, and concentrated under vacuum to give the crude product that was analyzed by ^{1}H NMR to determine the diastereoisomeric ratio. Flash chromatography with a 80:20 or a 70:30 hexanes:diethyl ether mixture as eluant gave the pure product in the yields reported in the text.

4.4. (±)-1,4-Di(4-methoxyphenyl)-3-(3-phenylpropyl)azetidin-2-one **1**

The title compound had spectral data in agreement with those reported.[8] Mp 96–98°C (lit.[8] 96–97.5°C).

4.5. (3S,4S,4′S)-1-(4-Methoxyphenyl)-3-(3-phenylpropyl)-4-[1-[[(1,1-dimethylethyl)dimethylsilyl]-oxy]ethyl]azetidin-2-one **8**

The title compound was a thick oil. It had $[\alpha]_D^{23}$ −31.3 (c 0.5 in CH_2Cl_2). IR: 1742 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 (2H, A part of AB system, J=8.7 Hz), 7.10–7.30 (5H, m), 6.87 (2H, B part of AB system, J=8.7 Hz), 4.19 (1H, q, J=6.2 Hz), 3.73 (1H, dd, J=6.0 Hz), 3.02 (1H, dt, J=6.2, 2.1 Hz), 2.68 (2H, t, J=7.1 Hz), 1.80–1.90 (4H, m), 1.14 (3H, d, J=6.0 Hz), 0.85 (9H, s), −0.05 (3H, s), −0.11 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.5, 155.0, 141.5, 132.0, 128.4, 125.0, 119.5, 114.2, 69.6, 62.9, 55.5, 51.3, 35.7, 28.9, 28.3, 19.2, 17.9, −4.2, −4.7. Elem. anal.: $C_{27}H_{39}NO_3Si$ requires: C, 71.48; H, 8.66; N, 3.09. Found: C, 71.67; H, 8.83; N, 3.02.

4.6. (3′R,3S,4S)-1,4-Di(4-methoxyphenyl)-3-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-phenylpropyl]-azetidin-2-one **12**

The title compound was a thick oil. It had $[\alpha]_D^{23}$ −39.4 (c 0.07 in $CHCl_3$). IR: 1740 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (2H, A part of AB system, J=8.7 Hz), 7.30 (2H, B part of AB system, J=8.7 Hz), 7.15–7.28 (5H, m), 7.08 (2H, A part of AB system, J=8.7 Hz), 6.94 (2H, B part of AB system, J=8.7 Hz), 5.15 (1H, d, J=2.4 Hz), 4.15 (1H, dt, J=7.4, 2.4 Hz), 3.82 (6H, s), 3.28 (1H, t, J=2.4 Hz), 2.54 (2H, t, J=8.1 Hz), 1.90–2.00 (2H, m), 0.82 (9H, s), 0.13 (3H, s), 0.07 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.7, 159.5, 155.7, 141.0, 130.2, 128.4, 128.3, 128.0, 125.9, 118.5, 114.5, 114.1 68.4, 65.2, 55.4, 55.3, 38.7, 31.6, 28.9, 25.7, 17.9, −4.2, −4.7. Elem. anal.: $C_{32}H_{41}NO_4Si$ requires: C, 72.27; H, 7.78; N, 2.63. Found: C, 72.49; H, 7.83; N, 2.58.

4.7. Attempted conversion of **8** to **1**. Synthesis of (3R,4R)-1-(4-methoxyphenyl)-3-(3-phenyl)propyl-4-acetoxy azetidin-2-one **9**

Compound **8** was desilylated in standard conditions with tetrabutylammonium fluoride in THF (see below for the synthesis of **2**) to give the alcohol in quantitative yield. The crude material was converted into the product following the procedure for the lead tetraacetate promoted oxidation described by Cainelli et al.[25] Compound **9** was obtained as a low melting solid. A 76:24 mixture of *trans* and *cis* isomers had $[\alpha]_D^{23}$ −13.4 (c 2.0 in CH_2Cl_2). IR: 1756, 1731 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) of major (*trans*) isomer: δ 7.35 (2H, A part of AB system, J=8.8 Hz), 7.25–7.35 (3H, m), 7.15–7.25 (2H, m), 6.90 (2H, B part of AB system, J=8.8 Hz), 6.19 (1H, d, J=1.1 Hz); 3.80 (3H, s), 3.23 (1H, dt, J=6.2, 1.1 Hz), 2.67 (2H, t, J=6.2 Hz); 2.13 (3H, s), 1.83–1.96 (4H, m). ^1H NMR (300 MHz, $CDCl_3$) of minor (*cis*) isomer: δ 7.35 (2H, A part of AB system, J=8.8 Hz), 7.25–7.35 (3H, m), 7.15–7.25 (2H, m), 6.90 (2H, B part of AB system, J=8.8 Hz), 6.61 (1H, d, J=4.3 Hz); 3.80 (3H, s), 3.50 (1H, dt, J=6.0, 4.3 Hz), 2.67 (2H, t, J=6.0 Hz); 2.08 (3H, s), 1.83–1.96 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$) of major (*trans*) isomer: δ 170.3, 165.2, 156.7, 141.6, 130.0, 128.4, 125.9, 118.5, 114.5, 80.1, 58.5, 55.5, 35.7, 28.5, 26.5, 23.8. ^{13}C NMR (75 MHz, $CDCl_3$) of minor (*cis*) isomer: δ 170.4, 165.3, 156.7, 141.6, 130.0, 128.4, 125.9, 118.5, 114.5, 76.9, 58.5, 55.5, 35.7, 29.0, 26.5, 23.9. Elem. anal.: $C_{21}H_{23}NO_4$ requires: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.47; H, 6.39; N, 3.88.

4.8. Synthesis of N-4-methoxyphenyl 2-(3-phenylpropyl)-3-hydroxy-3-(4-methoxyphenyl)propane amide **10**

A solution of **9** (0.172 g, 0.5 mmol) and $BF_3 \cdot OEt_2$ (0.064 mL, 0.5 mmol) in dry THF (10 mL) was added at −78°C to a stirred solution of 4-methoxyphenyllithium (2.5 mol equiv.) in THF (20 mL) kept under nitrogen. The mixture was warmed up to −40°C and stirred at that temperature for 5 h. The reaction temperature was allowed to rise to room temperature, and the stirring was continued for additional 5 h. The reaction was quenched by the addition of a satd aqueous solution of ammonium chloride. The organic phase was separated, dried, and concentrated under vacuum. The crude product was purified by flash chromatography with a 40:60 hexanes:diethyl ether as eluant to afford the product as a 75:25 mixture of diastereoisomers. The product was a waxeous solid. IR: 3400, 1610 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) of major isomer: δ 7.43 (1H, brs), 7.10–7.30 (9H, m), 6.78–6.90 (4H, m), 5.00 (1H, d, J=4.0 Hz), 3.81 (3H, s), 3.79 (3H, s), 3.33 (1H, brs), 2.55–2.65 (2H, m), 2.40–2.50 (2H, m), 1.50–1.90 (4H, m).^1H NMR (300 MHz, $CDCl_3$) of minor isomer: δ 7.33 (1H, brs), 7.10–7.30 (9H, m), 6.78–6.90 (4H, m), 4.91 (1H, d, J=6.0 Hz), 3.81 (3H, s), 3.79 (3H, s), 3.46 (1H, brs), 2.55–2.65 (2H, m), 2.40–2.50 (2H, m), 1.50–1.90 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$) of major isomer: δ 172.8, 159.1, 157.0, 142.1, 133.8, 130.4, 128.4, 127.5, 125.7, 122.2, 114.0, 74.1, 55.5, 55.4, 54.9, 35.9, 29.5, 26.3. ^{13}C NMR (75 MHz, $CDCl_3$) of minor isomer: δ 172.8, 159.1, 157.0, 141.2, 134.7, 130.4, 128.3, 127.3, 125.8, 122.3, 113.9, 75.1, 55.5, 55.4, 55.3, 35.9, 30.0, 29.3. Elem. anal.: $C_{26}H_{29}NO_4$ requires: C, 74.44; H, 6.97; N, 3.34. Found: C, 74.57; H, 6.90; N, 3.39.

4.9. Synthesis of (3′R,3S,4S)-1,4-di(4-methoxyphenyl)-3-[(1-hydroxy-3-phenyl)propyl]azetidin-2-one **2**

To a stirred solution of **12** (0.133 g, 0.25 mmol) dissolved in dry THF (5 mL), tetrabutylammonium fluoride trihydrate (0.158 g, 0.5 mmol) was added, and the resulting mixture was stirred overnight. The reaction was quenched with water. After addition of diethyl ether the organic phase was separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried and concentrated under vacuum to give a residue that was purified by flash chromatography with a 50:50

hexanes:diethyl ether mixture as eluant. The product (0.103 g, 99%) was a solid, mp 153–155°C; $[\alpha]_D^{23}$ −39.6 (c 0.5 in $CHCl_3$). IR: 3400, 1741 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.31 (4H, two A parts of AB systems, J=8.7 Hz), 7.20–7.30 (5H, m), 6.92 (2H, B part of one of the two AB systems, J=8.7 Hz), 6.78 (2H, B part of other of the two AB systems, J=8.7 Hz), 5.05 (1H, d, J=2.4 Hz), 4.50 (1H, brs), 4.18–4.26 (1H, m), 3.81 (3H, s), 3.75 (3H, s), 3.18 (1H, dd, J=5.2, 2.4 Hz), 2.82 (1H, A part of AB system, J=15.0, 8.6 Hz), 2.67 (1H, A part of AB system, J=15.0, 8.6 Hz), 1.92–2.02 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.0, 159.5, 156.0, 141.5, 131.5, 130.0, 128.6, 128.3, 126.0, 118.6, 114.6, 114.3, 68.1, 66.0, 56.2, 55.4, 55.2, 36.8, 31.9. Elem. anal.: $C_{26}H_{27}NO_4$ requires: C, 74.80; H, 6.52; N, 3.35. Found: C, 74.67; H, 6.69; N, 3.38.

*4.10. Synthesis of (3*R,*4*S*)-**1***

Synthesis of the activated ester: A mixture of **2** (0.100 g, 0.24 mmol) and thiocarbonyl diimidazole (0.190 g, 1.2 mmol) in dry THF (5 mL) was refluxed overnight. To the cooled mixture a satd aqueous solution of ammonium chloride was added, and the organic phase was separated. The aqueous phase was extracted twice with diethyl ether and the combined organic phases were dried and concentrated under vacuum to give the crude product that was purified by flash chromatography with a 70:30 hexanes:diethyl ether mixture as eluant. The product (0.094 g, 94%) was a solid, mp 150–152°C; $[\alpha]_D^{23}$ +20.5 (c 0.33 in $CHCl_3$). IR: 1746, 1098, 1028 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.55 (1H, brs), 7.50 (1H, brs), 7.23 (2H, A part of AB system, J=8.0 Hz), 7.17 (2H, A part of AB system, J=8.7 Hz), 7.10–7.20 (5H, m), 7.00 (1H, brs), 6.87 (2H, B part of AB system, J=8.7 Hz), 6.80 (2H, B part of AB system, J=8.0 Hz), 6.27 (1H, dt, J=7.6, 4.6 Hz), 5.02 (1H, d, J=2.4 Hz), 3.81 (3H, s), 3.76 (3H, s), 3.53 (1H, dd, J=7.6, 2.4 Hz), 2.73–2.83 (2H, m), 2.34 (2H, AB system, J=15.6, 8.0, 7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 183.5, 161.9, 160.0, 153.0, 140.1, 136.3, 131.0, 128.5, 128.2, 126.9, 126.3, 118.4, 117.9, 114.6, 114.4, 81.5, 63.3, 58.1, 55.4, 55.3, 33.9, 31.1. Elem. anal.: $C_{30}H_{29}N_3O_4S$ requires: C, 68.29; H, 5.54; N, 7.96. Found: C, 68.47; H, 5.69; N, 7.78.

Deoxygenation: To a stirred solution of the activated ester (0.052 g, 0.1 mmol) in dry DMSO (2 mL) kept at 90°C under nitrogen, freshly opened Bu_3SnH (0.087 g, 0.3 mmol) and AIBN (0.002 g) were added. The mixture was stirred for 4 h, while equal portions of AIBN were added every hour. The cooled reaction mixture was poured into water and extracted several times with diethyl ether. The combined organic phases were washed with brine, dried, and concentrated under vacuum to give the crude product that was purified by flash chromatography with a 50:50 hexanes:diethyl ether mixture as eluant. This purification allowed recovery of some of the unreacted activated ester. The product, a white solid, had analytical and spectral data identical to those reported in the literature: mp 46–48°C (lit.[8] 46.5–48°C); $[\alpha]_D^{23}$=−19.1 (c 0.1 in MeOH) (lit.[8] $[\alpha]_D^{23}$=−19.3 (c 6.23 in MeOH)).

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